PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: DT

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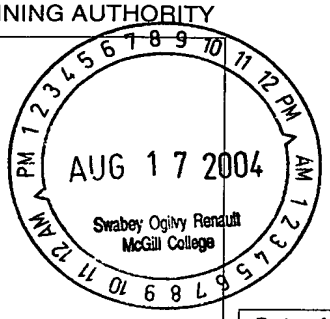


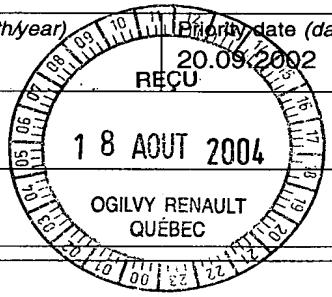
PCT
WRITTEN OPINION:
DUE ON OCT 12 2004
WRITTEN OPINION
(PCT Rule 66)
FAX 514 288 8389

Date of mailing *(day/month/year)*	12.08.2004
Applicant's or agent's file reference 6013-118PCT	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01269	20.08.2003	20.09.2002

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
UNIVERSITE LAVAL et al.



1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20.01.2005

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

1/28-28/28 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.
   ☒ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-15, 25 and 26 (all in part), 16-20 and 27-29 (in full) .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-20, 25-29
Industrial applicability (IA)	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the opinion

1. Sequence listing pages 1-40 are also included in the basis of this written opinion.

2. The description mentions figures 8d and 8e which however appear to have not been filed with the application (cf. description p. 24 line 12).

to be addressed Annual PT ?

Re Item IV

Following the observation that the present application lacks unity contrary to the requirements of Rule 13(1) PCT, an invitation to restrict the claims or to paid additional examination fees has been sent to the applicant on May 27th,2004.

Although, the applicant has neither restricted the claims nor paid additional fees, his resquest to limit the examination to the claimed subject-matter encompassed by the third invention, i.e. the subject-matter claimed in claims 1-15, 25 and 26 (in part), 16-20 and 27-29 (in full), has been taken into consideration and the present given opinion with respect to the provisions of Article 33(1) PCT (i.e. novelty, inventive step and industrial applicability) is given accordingly - i.e. only for claims 1-15, 25 and 26 (in part), 16-20 and 27-29 (in full) insofar as their subject-matter relate to UGT1A9 polymorphism.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: Tukey R. H. and Strassburg C. P. - 'Human UDP-glucuronosyltransferases: metabolism, expression, and disease' - 2000 - *Annual Review of Pharmacology and Toxicology*, **40**: 581-616

D2: Guillemette C. *et al.* - 'Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene' - 2000 - *Pharmacogenetics*, **10**: 629-644

D3: Gagné J.-F. *et al.* - 'Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-

38)' - *Molecular Pharmacology*, (09-2002), **62**(3), 608-617

2. Novelty (Article 33(2) PCT)

2.1 No prior-art document at hand discloses the subject-matters of claims 1-20 and 25-29, said claims thus meet the requirements of Article 33(2) PCT.

3. Inventive step (Article 33(3) PCT)

3.1 The subject-matters of claims 1 is not considered to involve an inventive step contrary to the requirements of Article 33(3) PCT, the reasons being as follows:

The considerable substrate-specific redundancy in phenolic glucuronidation between many of UGT1A enzyme isoforms including UGT1A1, UGT1A7 and UGT1A9, as well as the encoding gene sequences of said enzymes are very well known in the art and reported in document D1 (cf. D1 p. 594 line 37 - 596 line 42; p. 599 line 22 - p. 606 line 30; Fig. 1-4 and Table 2). Various polymorphisms in the genes encoding UGT1A enzyme isoforms such as UGT1A1 and UGT1A7 have been described and associated to reduced or modified enzymatic activities of said isoform in particular in their ablilities to act as detoxifying agents (see for example the whole disclosure of D2 and D3). Since only one gene locus encodes for all UGT1A enzyme isoforms, the gene encoding UGT1A9 isoform is therefore situated in the same locus as the genes encoding for UGT1A1 or UGT1A7 and it would therefore have been obvious to the skilled person that polymorphisms in the coding sequences of UGT1A9 are also existing, such a polymorphism is in fact already reported in D2 (cf. D2 p. 641 right-hand column 2nd §). Moreover, and as postulated in D2 as well as in D3 the skilled person knowing that such polymorphisms might be linked to a reduced enzymatic acivity phenotype (cf. D2 p. 641 right-hand column 2nd §; and D3 abstract and p. 617 left-hand column 1st §), would have been encouraged to test such hypothesis and therefore arrive to the method of claim 1 without the exercise of an inventive skill.

The subject-matter of claim 1 therefore does not involve an inventive step and claim 1 thus does not fulfill the requirements of Article 33(3) PCT.

3.2 In view of the prior-art documents at hand, dependent claims 2-20 do not appear to contain any additional features which, in combination with the features of any claim

to which they refer, meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT) since these additional features appear to be conventional and do not appear to result in any unexpected effect (Article 33(3) PCT).

3.3 For identical reasons as those exposed under point 3.1 above the skilled person without the exercise of inventive skills and by determining the sequences encoding the polymorphisms contained in UGT1A9 isoform using conventional technics of molecular biology would have arrived to the sequences disclosed in claims 25, 26 or 27-29. Therefore said claims are not considered to meet the requirements of Article 33(3) PCT.

4. Further comments

4.1 Claim 3 is drafted using vague expressions such as "a higher or lower susceptibility...constitutional sickness to said physiological reaction" which leave the reader in doubt as to the exact scope for which protection is sought (see PCT Guidelines Section IV, III-4.5). Claim 3 therefore lacks clarity (Article 6 PCT).